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ORIGINAL PAPER

Analysis of ocular inflammation in anterior chamber—involving uveitis using swept-source anterior segment OCT

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Abstract
Purpose To evaluate the utility of swept-source (SS) optical coherence tomography (OCT) to objectively analyze the degree of anterior chamber (AC) inflammation.
Methods Thirty-eight eyes of 32 patients with uveitis and 20 control eyes were enrolled. SS OCT B-scans were obtained, and the number of cells in the B-scans was counted using two methods: (1) manual grading by Point Picker plug-in of Image J (http://bigwww.epfl.ch/thevenaz/pointpicker/) and (2) automated grading by the Image J Particle Analysis algorithm (http://imagej.net/Particle_Analysis). The automated and manual AC cell counts were correlated with the Standardization of Uveitis Nomenclature score.
Results The average numbers of AC inflammatory cells counted by the automated method were 8 ± 4.0, 18 ± 3.0, 42 ± 14.0, 81 ± 32.0, 117 ± 57.0, and 275 ± 67.0 cells/mm^2 for grades 0, 0.5 + , 1 + , 2 + , 3 + , and 4 + , respectively. For the same clinical categories, the average manual cell counts were 6 ± 4.0, 18 ± 3.0, 34 ± 14.0, 72 ± 32.0, 92 ± 43.0, and 168 ± 65.0 cells/mm^2, respectively. Zero cells were detected in the AC of healthy eyes. The automated and manual methods were highly correlated (R = 0.98, $p < 0.001$) and showed good correlation with the clinical grading (R = 0.88, $p < 0.001$). A mean AC particle size of 117.4 ± 108.8 µm was obtained by the automated method.
Conclusions Quantification of the AC cells imaged by SS AS-OCT shows good correlation with categorical clinical severity assessments in uveitis eyes. This approach may provide a more objective method for monitoring uveitis and response to uveitis therapy.

Keywords Imaging · Uveitis · Swept-source optical coherence tomography · Clinical grading

Introduction

Uveitis encompasses a group of intraocular inflammatory disorders with infectious or autoimmune etiology [1]. It affects people of any age, but the highest prevalence is in adults of working age [2]. According to the anatomical classification, about 30–60% (average 47%) are categorized as anterior uveitis, which is characterized by the presence of inflammatory cells in the anterior chamber (AC). [1, 2] Panuveitis requires involvement of all anatomical

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compartments of the eye: the AC, vitreous, and retina or choroid with no predominant site of inflammation.

According to Standardization of Uveitis Nomenclature (SUN) Working Group, slit-lamp bio-microscopy is the standard of care to grade AC cells using on an ordinal severity scale of 0–4 + [3]. This standardized method heavily relies on subjective evaluation of the number of cells visualized by the observer and thus is susceptible to inter-observer variation [4]. Inter-observer variation combined with differences in devices and lighting conditions further affects the ability to consistently quantify cells in the AC, especially for multicenter clinical trials [5]. Grading with laser flare photometry has been investigated and used in some studies, but its accuracy and utility in determining AC flare remain uncertain [6, 7].

Due to existing challenges in consistently grading AC inflammation, a more objective method to evaluate the severity of AC inflammation is needed. Thus far, there is no universally adopted method to quantify AC cellular reaction. Anterior segment optical coherence tomography (AS-OCT), either time or spectral domain, has been studied to image different aspects of the anterior segment (AS), including AC inflammation [8–12]. Commercially available AS-OCT devices feature different axial and transverse resolutions. Among them spectral-domain optical coherence tomography (SD-OCT) devices have finer axial and transverse resolutions in tissue than time-domain (TD) OCT [13]. AC imaging has been improved with the introduction of swept-source optical coherence tomography (SS AS-OCT). This technology provides high resolution (< 10 μm), ultrafast speed (> 100.000 A-scans/s.), sufficient ranging distance (> 12 mm), as well as rapid acquisition of three-dimensional (3-D) OCT data of the whole segment within an acceptable time frame [14]. Increase of scanning speed in SS OCT technology may decrease the propensity for motion artifact, which can be used as an advantage to measure and report cell size on single-line scans. Additionally, a 3-D reconstruction OCT map of the AC can be useful to analyze the total number of cells in the AC along with cell density per mm^3.

The purpose of our study was to evaluate the utility of higher resolution SS AS-OCT to objectively image and quantify inflammatory reaction in the anterior chamber.

Materials and methods

Subjects and clinical examination

This was an observational, prospective, consecutive case series of patients presenting to the Uveitis Clinic at the Doheny Eye Center-UCLA in Pasadena, California, with a uveitis diagnosis between December 2015 and January 2017. Study approval was granted by the Institutional Review Board of the University of California, Los Angeles, and was carried out in agreement with the tenets of the Declaration of Helsinki of 1964, as revised in 2013. Written informed consent was obtained for all study subjects.

A detailed slit-lamp examination in addition to general ophthalmological evaluation was carried out for all subjects by a single uveitis specialist (OLL). The clinical degree of AC inflammation was evaluated using SUN nomenclature [3]. The clinical grading was performed before the AS-OCT imaging.

The main inclusion criteria were the presence of AC—involving uveitis (active or inactive) in one or both eyes.

In addition to uveitis eyes, 20 normal eyes of ten control subjects without any ocular inflammation, history of uveitis, ocular surgery or trauma, or ocular diagnosis other than refractive error were recruited as well. Any eye without corneal clarity was excluded.

Anterior segment optical coherence tomography imaging

All patients were imaged using the DRI Triton (Topcon, Tokyo, Japan) by three operators (EB, JH, and PH) masked to the diagnosis and clinical grading results. This SS OCT device, fitted with a corneal adaptor module, was used to image the cornea and anterior segment of the eye. The device operates at a speed of 100,000 A-scans/second and uses a light source wavelength of 1050 nm. Per the manufacturer specifications, with this configuration, technical specifications include an axial resolution of 8 μm, lateral resolution of 20 μm, a lateral scan dimension from 3 to 16 mm, and a 2.6-mm scan depth in tissue (axial direction) for cornea and AC imaging. Tracking can also be engaged for anterior segment imaging. For this study, a 3-mm horizontal single-line B-scan (1024 A-scans) protocol with 64 × averaging was used to image central cornea corresponding to the hyper-reflective reflex seen on the scan (i.e., at the corneal apex) [15]. Although the posterior cornea boundary is well seen with this protocol, the iris or lens is not captured with this axial scan depth of 2.6 mm. Acceptable images had clear and sharp focus, few to no artifacts (motion lines) and signal strength 55 and higher with averaging success rate of 54/64 and higher. Poor-quality scans which did not meet these criteria were re-acquired. Scanning was repeated until a minimum of three sufficient quality scans were obtained, and these acceptable scans were exported at a size of 1024 × 896 pixels (eight-bit gray scale) for AC cell analysis.

Manual and automated grading

AS-OCT B-scan images were imported and analyzed using online public-domain software, Image J (available at http://rsb.info.nih.gov/ij, developed by Wayne Rasband, National Institutes of Health, Bethesda, MD). In particular, we utilized the automated particle analysis program of Image J (for automated analysis) and the Point Picker plug-in of Image J (for manual cell counts).

Pixels were converted to micrometers after opening images in Image J software (2.93 µm/pixel was provided by the manufacturer and subsequently used to set the scale). The rectangular area with a dimension of 2500 × 550 µm was selected as an optimal size to crop the region of interest within the central AC in all the B-scans in order to exclude the cornea. This step effectively isolates the region of interest within the AC for subsequent cell count analysis.

Particle analysis, both manual and automated, was performed on the inverted grayscale images. A default thresholding method was set to differentiate hyper-reflective foci corresponding to inflammatory cells from the background aqueous. Subsequently, a watershed function was employed to separate overlapping spots. To analyze particles in the binarized image, we used the menu command *Analyze Particles* that provided us with particle (cell) counts and size. Particle size was analyzed using the automated method as the manual method was deferred.

The manual grading of AC cells was also performed on these binarized images. Each of the high-resolution single-line scans was evaluated by a single trained Doheny Image Reading Center grader (EB) masked to the clinical grades. The values for the hyper-reflective foci count from the three scans were averaged to yield a final value from the manual and automated methods for each case.

Statistical analysis

Spearman's rank correlation was used to measure the correlation between the clinical and OCT grading as well as between the two (manual vs automated) grading methods. Additionally, analysis of variance (ANOVA) test was performed to test the repeatability of the measurements obtained on each eye. Statistical analysis was performed using SPSS version 15.1 software package for Windows (SPSS Inc., Chicago, Illinois, USA) and MedCalc version 14.8.1 (MedCalc Software, Mariakerke, Belgium). A positive correlation between the clinical and AS-OCT grading was considered significant when $R \geq 0.5$ with $p < 0.05$.

Results

Clinical demographics

Thirty-eight eyes of the 32 patients (12 F and 20 M) were diagnosed with AC-involving uveitis (either anterior uveitis or panuveitis) due to a variety of etiologies (Table 1). The average age of the patients was 52 ± 21.0 years (range 11–86 years). Twenty eyes (53%) were assigned a grade of 0 according to SUN criteria, two eyes (5%) had a grade of 0.5 + AC cells, three eyes (8%) with 1 + , four eyes (11%) with 2 + , six eyes (15%) with 3 + , and three eyes (8%) with 4 + (Table 2). A total of 20 eyes from ten control subjects (10 F and 10 M) were enrolled as well. Their average age was 32.3 ± 4.8 years (range: 24–42 years).

SS AS-OCT 3 mm horizontal single-line scan results

Zero AC inflammatory cells were detected in all 20 control eyes (clinically having grade 0 AC cells by SUN grading scale) using both the manual and automated methods (Fig. 1).

As shown in Table 2, within the uveitis cohort, there was a mean of 8 ± 4.0 cells/mm^2 for grade 0 eyes, 18 ± 3.0 cells/mm^2 for grade 0.5 + , 42 ± 12.0 cells/mm^2 for grade 1 + , 81 ± 32.0 cells/mm^2 for

Table 1 Diagnosis of AC—involving uveitis in our cohort

Diagnosis of uveitis	Number of patients	Number of eyes
Idiopathic anterior uveitis	16	20
HLA B27-associated anterior uveitis	4	6
Sympathetic ophthalmia	1	1
VKH	1	1
Pars planitis	2	2
HSV-associated anterior uveitis	1	1
JIA	2	2
Traumatic iritis	3	3
Postoperative inflammation	2	2

HLA B27 human leukocyte antigen, *HSV* herpes simplex virus, *VKH* Vogt-Koyanagi-Harada, *JIA* juvenile idiopathic arthritis

Table 2 Clinical severity evaluation with corresponding automated and manual average cell counts from 3-mm single-line SS AS-OCT B-scans

Clinical grade	Average number of (cells/mm^2) (automated)	Average number of (cells/mm^2) (manual)	Number of eyes (%)
0+	8.0 ± 4.0	6.0 ± 4.0	20 (53%)
0.5+	18.0 ± 3.0	18.0 ± 3.0	2 (5%)
1+	42 ± 14.0	34 ± 14.0	3 (8%)
2+	81 ± 32.0	72 ± 32.0	4 (11%)
3+	117 ± 57.0	92 ± 43.0	6 (15%)
4 +	275 ± 67.0	168 ± 65.0	3 (8%)

Data presented as mean ± standard deviation

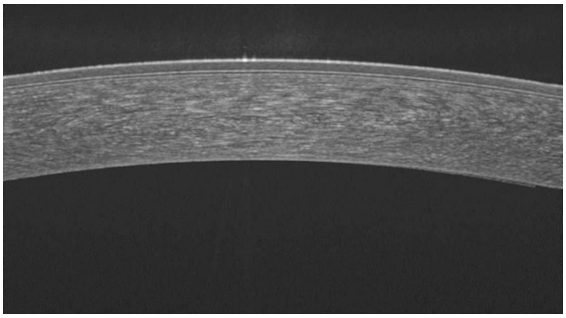

Fig. 1 Representative SS AS-OCT B-scan image from control eye showing absence of hyper-reflective foci in the aqueous

grade 2 + , 117 ± 57.0 cells/mm^2 for grade 3 +, and 275 ± 67.0 cells/mm^2 for grade 4 + detected using the automated analysis method. The manual method revealed 6 ± 4.0 cells/mm^2 for grade 0, 18 ± 3.0 cells/mm^2 for grade 0.5 + , 34 ± 14.0 cells/mm^2 for grade 1 + , 72 ± 32.0 cells/mm^2 for grade 2 + , 92 ± 43.0 cells/mm^2 for grade 3 +, and 168 ± 65.0 cells/mm^2 for grade 4 + (Table 2). The automated and manual measurements of the AC cell count across the three B-scans were repeatable with p value > 0.05 (Table 3). Representative SS AS-OCT B-scan images for grades 0, 0.5 +, 1 + , 2 + , 3 +, and 4 + AC cells are shown in Fig. 2.

Average particle size from the automated analysis method was 117.4 ± 108.8 µm (range: 10–383.5 µm).

The Spearman correlation coefficients were $R = 0.88$ (95% confidence interval [CI] 0.7873–0.9376; $p < 0.001$) and $R = 0.88$ (95% CI 0.7822–0.9360; $p < 0.001$) for the automated and manual methods compared with the clinical grading, respectively (Figs. 3 and 4). The Spearman's correlation coefficient was $R = 0.98$ (95% CI 0.9553–0.9877; $p < 0.001$) when comparing the manual and automated methods (Fig. 5).

Discussion

SUN working group recommended a consensus standard method for rating the severity of AC inflammatory cells and flare [3]. This system has limitations,

Table 3 Repeatability of the AC cell count derived from three sequential single-line SS AS-OCT B-scan images analyzed by the Image J automated and manual methods. Data presented as mean ± standard deviation

Methods	AC cell count (cells/mm^2) (1st measurement)	AC cell count (cells/mm^2) (2nd measurement)	AC cell count (cells/mm^2) (3rd measurement)	ANOVA (p value)
Automated analysis	57 ± 82	55 ± 81	54 ± 80	0.98
Manual analysis	42 ± 56	40 ± 55	41 ± 56	0.98

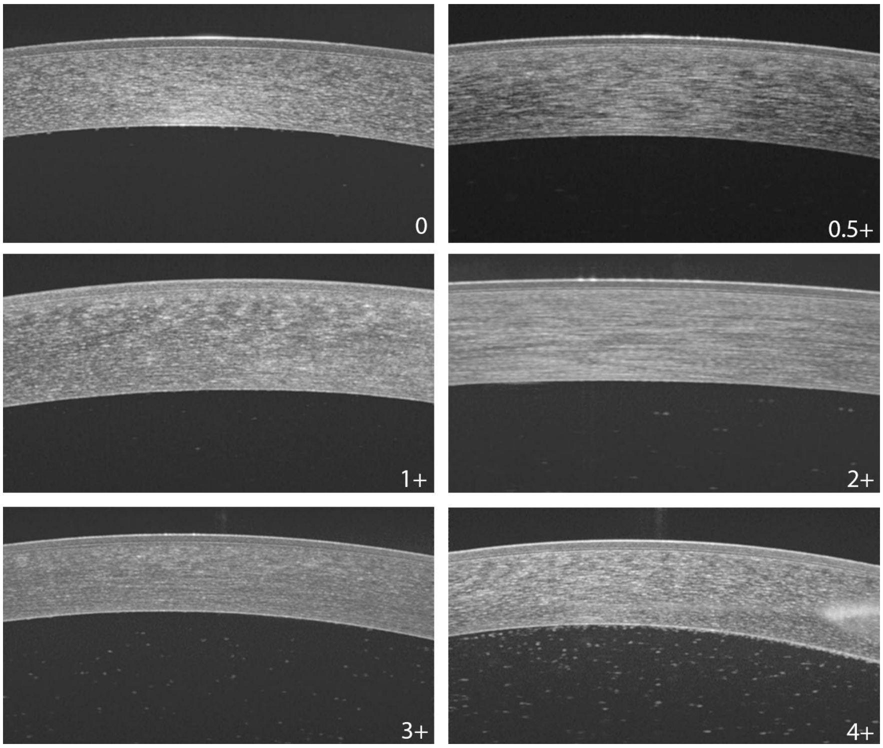

Fig. 2 Representative SS AS-OCT B-scan images from eyes of uveitis patients at each clinical grade severity level 0–4 + . The central cornea is positioned at the superior aspect of each B-scan. Hyper-reflective foci in the aqueous are thought to represent anterior chamber (AC) cells

namely inter-observer variability. Subjectivity of clinical grading despite the consensus standard results in an additional source of variability that is suboptimal for clinical trials.

According to the SUN working group, improvement in inflammation is defined as either a two-step decrease in the level of inflammation, or a decrease to inactive, while worsening is defined as two-step increase in the level of inflammation, or an increase to the maximum level. Ultimately, this categorical scale is subjective, has limited precision, and may not be consistently applied from clinician to clinician. A quantitative scale, if shown to be reproducible, could be of value in refining the assessment of treatment endpoints and response, both in clinical practice and in clinical trials. Such a rating system could be of particular value if the severity score could be obtained in an automatic fashion. An additional advantage of a quantitative value over clinical grading scale is that the numerical value could be compared longitudinally in a more granular fashion.

A major advantage of OCT-based assessment of AC inflammation is that quantitative parameters can be produced. Cell density (cells/mm$^{3)}$ is a useful marker of inflammation that can be assessed on OCT B-scans. Compared to data derived from the ordinal SUN grading scale, cell density quantification allows for numerical data to be analyzed with greater degree of statistical accuracy. Small degrees of change in AC inflammation can be detected by quantifying cell density, which would not be detected unless there was a change in cellular reaction great enough to warrant a

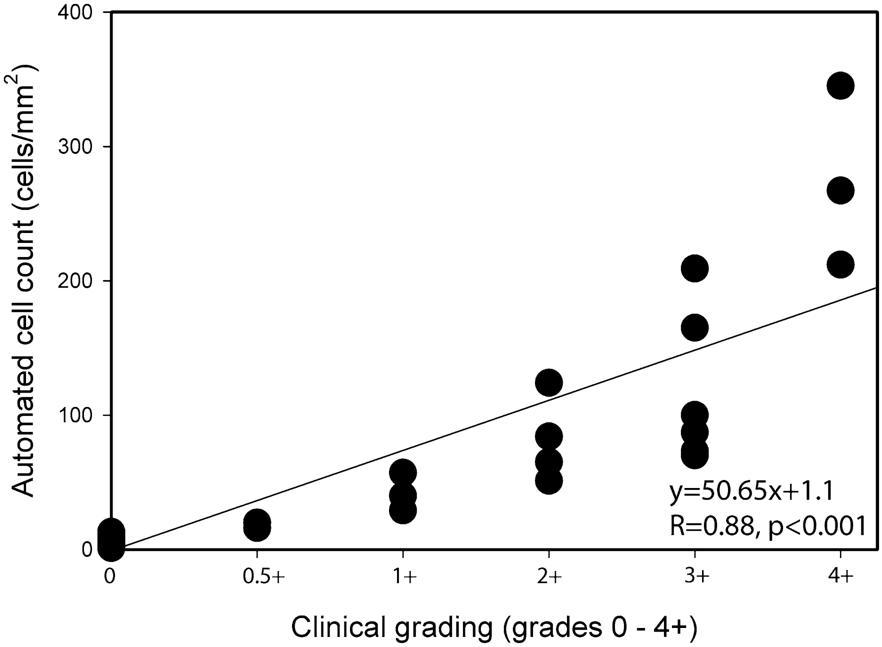

Fig. 3 Plot of automated cell counts per mm^2 versus clinical severity grading. Variability in the number of cells increases with a higher clinical severity grade. A positive statistically significant correlation is observed with a $R = 0.88$ and $p < 0.001$

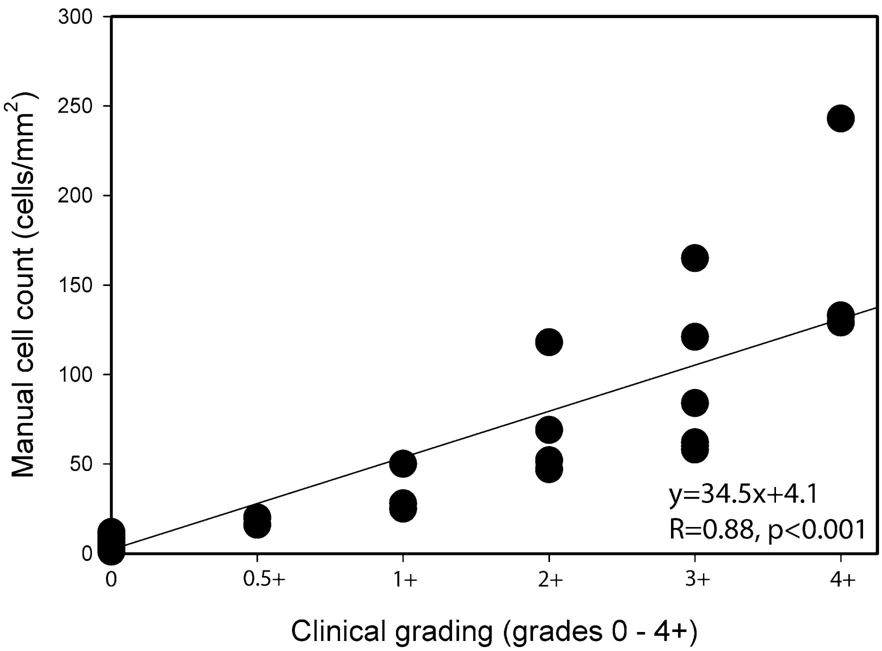

Fig. 4 Plot of manual cell counts per mm^2 versus clinical grading. Variability in the number of cells increases with higher clinical severity grade. A positive statistically significant correlation is observed with $R = 0.88$ and $p < 0.001$

stepwise change in the SUN grading scale. The SUN grading scale does not differentiate between those quiet uveitic eyes and control eyes, as both were clinically judged to have 0 cells by SUN grading scale. The cell density generated by analysis of OCT images demonstrated 4–12 cells/mm^2 in the uveitic eyes with 0 cells by clinical grading. Therefore, the OCT has the power to detect subclinical AC inflammation. This ability for detection of subtle changes may not be as relevant for clinical use, but would be helpful in clinical trials to detect and compare changes with therapy in large numbers of eyes.

Previous study of volumetric scans using OCT has shown excellent correlations between automatic and

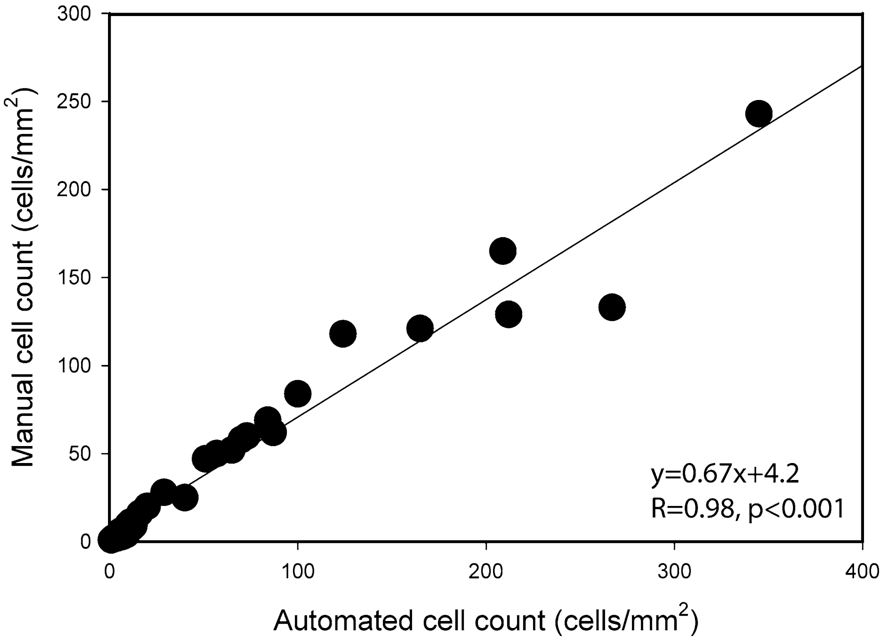

Fig. 5 Plot of manual versus the automated cell counts per mm^2. A strong positive statistically significant correlation is shown with $R = 0.97$ and $p < 0.001$

manual AC cell counts [12]. In previous studies, a significant positive correlation has been observed between clinical grading and OCT-based evaluation of the AC inflammatory cells [8, 10, 12, 20]. The present study not only replicates that correlation, but also evaluates OCT-based manual and automated grading of the AC inflammation.

AS-OCT is a noncontact imaging technique that allows micrometer-scale imaging of biological tissue. Various studies utilizing TD and SD-OCT scans of the AC have demonstrated a high degree of correlation with clinical SUN grading of AC inflammation [8, 10, 12, 16]. Our study has evaluated the utility of an SS AS-OCT system for objective rating of AC inflammation. Swept-source OCT may have important advantage over SD-OCT for these types of assessment. The faster speed of SS-OCT may reduce motion-related artifact—this may be particularly important in order to assess cell/particle size. In addition, SS OCT is more sensitive than SD-OCT with less roll-off in the sensitivity with depth. This is important as cells deeper in the AC may be seen as well as cells in the more anterior portion of the AC, which will be important for accurate quantification. Moreover, SS OCT devices use a longer wavelength (1050 nm) than SD-OCT ~ 840 nm, which allows for deeper imaging into the eye. Although there are AS TD-OCT devices with an even longer wavelength (~ 1310 nm), this is associated with a loss of axial resolution. [17] The stated axial resolution of the Topcon SS OCT system is 8 μm, which should be sufficient for capturing inflammatory cells in the AC. The average size of relevant inflammatory cells (neutrophils, lymphocytes, monocytes) is in the range of 10–20 μm [18]. Human iris pigment epithelium cells displaced into the AC have been reported to appear as black spheroids of average 24.4 μm in diameter, with a tendency to cluster (3–12 cells) and form aggregates of approximately 290 μm in diameter [19]. In our study, using our analysis methods, we have been able to identify AC particles as small as 10 μm and conglomerates as large as 383.5 μm in diameter. Thus, we would expect that our imaging strategy is effective at detecting the cells at the lowest end of the size range. Nevertheless, the larger particles we detected (up to 383 μm) could not represent a single cell. The presence of these structures could be explained by clustering or precipitation of cells, pigment, fibrin, or other inflammatory debris. The identification and differentiation of these require further investigation.

Although AS SS-OCT-based quantification of AC inflammation appears promising, several potential limitations must be considered. When evaluating a patient with slit-lamp bio-microscopy, clinicians may be able to use color criteria to distinguish white inflammatory cells from pigmented cells. This is of clinical relevance as pigmented cells may be a reflection of prior, but not active inflammation and may confound disease activity rating using OCT. Clinically, liberated iris pigment and pigmented inflammatory cells can be difficult to differentiate. Our study suggests that differences in the size and/or shape of the foci could be detected using OCT, which may be clinically useful to differentiate between these various types. This requires further research and validation. This also underscores another limitation of our present study in that we only focused on a few quantitative parameters (number of cells and particle size). It is possible that other parameters such as shape or particle distribution may be of importance when describing disease activity. Another limitation of our present study is that we based our assessment on single B-scan as opposed to a volume scan of the entire anterior chamber. We relied on the fact that such a sample would be representative of the entire anterior chamber, but that may not be an accurate assumption in all cases, as the distribution of cells in the AC can be uneven due to the aqueous fluid dynamics inside the AC [9, 12]. Other scan patterns and scans from different locations of the AC may need to be evaluated to establish the reliability of this approach. On the other hand, current slit-lamp-based SUN grading also assesses only a very small portion of the AC. Finally, our analysis thus far is based on a cross-sectional assay of a small cohort. Larger longitudinal studies will be necessary to validate whether an automated quantitative OCT-based approach can be used for assessment of treatment response over time.

In summary, in this study, we have been able to demonstrate that an AS SS-OCT device could be used to image, detect, and quantify cells in the AC in eyes with uveitis. This imaging technique is easily acquired in a noncontact fashion. The resulting images can be used to generate quantitative data describing AC cellular density and cell size. We show that such measurements correlate with clinical SUN severity grading. The potential of AS SS-OCT-based evaluation of uveitis warrants further study; however, the possibility of its usefulness in accurately and quantitatively assessing AC inflammation is suggested by the present study.

Compliance with ethical standards

Conflict of interest Elmira Baghdasaryan, Tudor C. Tepelus, Jianyan Huang, and Ping Huang declare no conflict of interest. SriniVas R. Sadda declares conflict of interest in Carl Zeiss Meditec (F), Optos (F, C), Allergan (F, C), Genentech (F, C), Alcon (C), Novartis (C), Roche (C), Regeneron (C), Bayer (C), Thrombogenics (C), Stem Cells Inc. (C), Avalanche (C). Olivia L. Lee declares no conflict of interest.

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